IN THE DRAWINGS:

A replacement sheet is attached hereto for Fig. 5(a), Fig. 5(b), Fig. 5(c), and Fig. 5(d). Fig. 5(d) has been corrected to illustrate the formulation 1240 as described in the Specification.

REMARKS

The Examiner is thanked for the very thorough and professional Office Action. Pursuant to that Office Action, Claim 2 has been cancelled, and Claims 3, 4, 10 and 12 rewritten to more definitely set forth the invention and obviate the rejections. Claims 3, 4 and 10 have been rewritten to change the dependency of these claims. Claim 12 has been amended in accordance with the Examiner's suggestions. Further, a replacement sheet containing Figs 5(a), Fig. 5(b), Fig. 5(c), and 5(d) is attached hereto. The present amendment is deemed not to introduce new matter. Claims 1 and 3-20 remain in the application.

Reconsideration is respectfully requested of the objection to the drawings as failing to show a formulation 1240 comprising the multipoint. A replacement sheet containing Figs. 5(a), 5(b), 5(c), and 5(d) is submitted herewith showing, in Fig. 5(d), the formulation 1240. This replacement sheet of the drawing is believed to obviate the objection and it is therefore believed that the objection is moot. Withdrawal of the objection to the drawings is respectfully requested.

Reconsideration is respectfully requested of the objection to Claim 10 under 35 U.S.C. 112, second paragraph, as being indefinite. The dependency of Claim 10 has been changed to Claim 7 which references the membrane. It is therefore believed that the objection is moot. Withdrawal of the objection is accordingly respectfully requested.

Reconsideration is respectfully requested of the rejection of Claim 12 under 35 U.S.C. 101 as being directed to non-statutory matter. Claim 12 has been amended in accordance with the Examiner's suggestion which is believed to obviate the rejection. Withdrawal of the rejection is accordingly respectfully requested.

Reconsideration is respectfully requested of the rejection of claims 1, 2 and 12 under 35 U.S.C. 103(a) as being unpatentable over Crawford, et al. in view of Howey.

Background

The technical level at the time of filing of this application regarding "the percutaneous or transmucosal administration" for a drug using iontophoresis and electroporation is, under the current circumstances, known to be difficult to deliver compounds with a molecular weight of more than 3000 by the combined use of electroporation and iontophoresis. Furthermore, it is also difficult to deliver a sufficient amount of insulin, which has a molecular weight of 6000, through the skin or mucosa " as a result of the discussion in the several documents mentioned in the specification (see Specification, page 3, lines 22-27). Since a molecular weight of insulin lispro is the same to that of human insulin (molecular weight: 5807), according to the technical level mentioned above, one of ordinary skill in the art would believe that it would be difficult, if not impossible, to deliver a sufficient amount of insulin lispro, even if the combined electroporation and iontophoresis are used.

The Present Invention

On the other hand, the present inventors attempted to administer various types of insulin, using iontophoresis and electroporation, singly or in combination (see Specification, page 4, lines 7-14). As a result, it was unexpectedly discovered that when insulin lispro is administered using electroporation with iontophoresis, excellent percutaneous or submucous absorptivity of the drug can be achieved. It was also unexpectedly discovered that insulin lispro exhibits sufficient beneficial effects and maintains such effects for a long time, thereby completing the present invention (see Specification, page 4, lines 15-24).

The Rejection

In the rejection, the Examiner relies upon the principal reference of Crawford, et al. for the disclosure of using both iontophoresis and electroporosis to distribute therapeutic agents.

To cure the deficiencies of the primary reference of Crawford, et al., the Examiner relies upon the secondary reference of Howey, et al. for the proposition that "it is known to use insulin lispro in the place of insulin, and that it would have been obvious to one of ordinary skill in the art to use insulin lispro as taught by Howey since "such modification could be an equivalent substance".

Argument

It is respectfully submitted that the rejection raises a number of important factual and legal issues as follows:

1. Whether the references considered as a whole provide a correct factual basis for the rejection as set forth by the Examiner.

2. Whether any prima facie case of obviousness is refuted by objective evidence (secondary considerations) of non-obviousness, and

3. Whether the rejection fails, as a matter of law, for failing to comply with the factual inquiries set forth in Graham v. John Deere Co., 383 US 1, 148 USPQ 459 (1966).

Applicants respectfully submit that the answer to these issues is in the negative with respect to the first issue, and in the affirmative with respect to the second and third issues, for the reasons discussed as follows.

The Crawford, et al. Reference

Crawford, et al. disclose delivering drugs, pharmaceuticals, plasmids, genes and other agents into living bodies using the combination of iontophoresis and electroporation. In this

connection Crawford,et al. disclose numerous human maladies for which drugs are delivered, including open heart surgery and chemotherapy (column 3, lines 24-48, and column 5, lines 1-7).

However, there is no disclosure whatever in Crawford, et al. of combining iontophoresis and electroporation in the treatment of diabetes, nor is there any disclosure of administering either human insulin or synthetic analogs of human insulin for the treatment of diabetes. In view of the known difficulty of administering a high molecular weight compound with a molecular weight of almost 6,000 using either electroporation or iontophoresis, it is respectfully submitted that one of ordinary skill in the art with only the Crawford, et al. reference before them would not consider it obvious to combine iontophoresis and electroporation for the treatment of diabetes with lispro. On the contrary, it is respectfully urged that one of ordinary skill in the art would not use electroporation or iontophoresis for treating diabetes because of the difficulty in delivering a sufficient amount of lispro by this method of administration.

The Howey, et al. Reference

In the rejection the Examiner argues that Howey, et al. teach that "it is known to use insulin lispro in place of insulin". It is respectfully submitted that Howey, et al. neither teaches this simple replacement, nor does Howey et al. teach that insulin lispro is an equivalent substance for insulin. Instead, Howey, et al. describe a clinical study designed to compare lispro with human Regular insulin after subcutaneous injection in humans. This study was conducted to evaluate the effect of adding zinc to lispro on its pharmacokinetics and pharmacodynamics.

To carry out this study, ten healthy (non-diabetic) men were treated both subcutaneously and intravenously with zinc-free lispro, zinc-containing lispro, and human regular insulin, given both subcutaneously and intravenously.

As pointed out in the "DISCUSSION" on page 399, and extending over through page 401 of Howey:

"These studies demonstrate that LYSPRO produces a significantly different pharmacokinetic and pharmacodynamic profile from that offered by Human Regular insulin after subcutaneous injection. Serum concentrations of LYSPRO peaked more than two times higher and in less than half the time of Human Regular insulin. At the same time, the glucose infusion rate peaked in about half the time and slightly but not significantly higher";

"--- LYSPRO had a shorter half-life in comparison to subcutaneously injected human Regular insulin but similar to that of intravenously administered Regular insulin"; and

"In conclusion, the absorption rate of LYSPRO with or without additional zinc is significantly more rapid than that of human Regular insulin after subcutaneous injection. With its more rapid absorption and shorter duration of action, LYSPRO may offer an advantage over human Regular insulin in the control of blood glucose after meals."

In view of the more complete disclosure of Howey, et al. above, it is respectfully submitted that LYSPRO is not considered an equivalent substance for insulin because it exhibits pharmacokinetics and pharmacodynamics different from insulin. Although Howey, et al. disclose that LYSPRO might be used in the treatment of diabetes, it is respectfully urged that Howey, et al. does not disclose the use of LYSPRO as a substitute for or equivalent to the effect of insulin in controlling blood glucose after meals. On the contrary, the data developed by Howey, et al. demonstrates, for example, that the mean glucose infusion rate for LYSPRO differs from that of the human Regular insulin administered subcutaneously and intraveneously. See data plotted in Figs. 3 and 4 on page 400 of Howey, et al.

In view of this more thorough analysis of Howey, et al., it is believed that the factual basis of the Examiner's rejection is erroneous because Howey, et al. make it clear, based on clinical studies, that LYSPRO does not have the same pharmacodynamics and pharmacokinetics as insulin. Therefore, it is equally clear that LYSPRO is not equivalent to insulin as contended by the Examiner. For this reason, it is believed that the Examiner would be justified in no longer maintaining this rejection.

Objective Evidence Of Non-Obviousness

In determining whether the subject matter as a whole is obvious, all evidence erring on the subject must be considered. *In re Soni*, 54 F3d 746 (CAFC 1995). Proof of an unexpected improvement can rebut a prima facie case of obviousness. *In re Murch*, 175 USPQ 89 (CCPA 1972).

No matter how strong the prima facie case of obviousness made out by the U.S. PTO, it must be weighed by any factors to the contrary brought out by the applicant in determining the validity of the conclusion of patentable unobviousness. *In re Lewis*, 170 USPQ 84 (CCPA 1971).

In the present case, the application sets forth numerous examples and comparative examples in which electroporation-iontophoresis as well as iontophoresis individually and electroporation individually were used in the administration of insulin and lispro. In Example 1 and comparative examples 1 and 2, a solution containing approximately 500 units of insulin lispro was used. In comparative example 3, a human insulin solution was used having a concentration of approximately 500 units/mL. In Example 2 and comparative example 4, a commercially available 100 units/mL Humalog was used.

Further, in comparative examples 5-7, various types of insulin were adjusted to have a concentration of 200 units/mL. An insulin-administering device containing these formulations was used to administer to the abdominal region of SD rats. Blood was collected from the carotid

arteries of the rats over time, and the level of insulin lispro in the blood and the level of glucose therein were measured.

In Example 2 an experiment was carried out in the same manner as Example 1, except that the unit of the insulin lispro solution administered was set at 100 units/mL.

In Comparative Example 1, only iontophoresis was used in the administration. In Comparative Example 2, only electroporation was used. In Comparative Example 3, only human insulin was used. In Comparative Example 4, only human insulin was used, and in Comparative Example 5, only swine insulin was used. In Comparative Example 6, bovine insulin was used. In Comparative Example 7, arginine insulin was used. The data obtained from these tests and measurements was then plotted in graphs.

Each of Examples 1, 2, and Comparative examples 3-7, uses the combined electroporation and iontophoresis.

Fig. 9 is a graph showing the level of insulin in the blood in Example 1 (insulin lispro) and Comparative example 3 (human insulin). Fig. 10 is a graph showing a change in the level of glucose in the blood in Example 1 and Comparative example 3, as a ratio of the blood glucose level after administration to the blood glucose level at the initial stage (before administration). According to Figs. 9 and 10, it was found that, although electroporation and iontophoresis are used in combination, sufficient absorption cannot be achieved unless a drug to be administered is insulin lispro.

Fig. 11 is a graph showing the level of insulin in the blood in Example 2 (insulin lispro) and Comparative Example 4 (Humalin). According to Fig. 11, it is found that, even though the concentration of insulin administered in Example 2 was set at one-fifth (1/5) of the concentration in Example 1, the maximum blood insulin level was approximately 700 μU/mL, and thus, when

compared with Comparative Example 4, extremely high absorption of insulin was achieved in Example 2.

Fig. 12 is a graph showing a change in the level of glucose in the blood in Example 2 (insulin lispro) and Comparative examples 4 (Humalin), 5 (swine insulin), 6 (bovine insulin), and 7 (arginine-insulin), as a ratio of the blood glucose level after administration to the blood glucose level at the initial stage (before administration). According to Fig. 12, it is found that, only in the case of using insulin lispro, the glucose level was decreased to 20% of the initial value, but when other types of insulin were used, a decrease in the glucose level was only 65% of the initial value.

It is respectfully submitted that this experimental data confirms that unexpectedly high absorption of insulin can be achieved only when insulin lispro is administered by using in combination the electroporation capable of applying a high electric field for a very short time and iontophoresis capable of applying a low electric field for a longer period. Also, high beneficial effects were confirmed by this data. When either the iontophoresis or the electroporation was used individually, no effects could be obtained. Although both means were used in combination, absorption was insufficient in the case of administering other types of insulin other than insulin lispro.

It is, therefore, respectfully submitted that these tests demonstrate the unexpected results obtained by the combined use of electroporation and iontophoresis to enable significantly high absorption of insulin lispro, when it is administered percutaneously or transmucosally.

In view of these startling and unexpected findings, it is respectfully urged that this objective evidence rebuts any prima facie case of obviousness made out by the Examiner's combination of references. For these reasons, the rejection fails, as a matter of law, in view of the

above authorities. Consequently, the Examiner would be justified in no longer maintaining the rejection. Withdrawal of the rejection is accordingly respectfully requested.

The Rejection Fails To Comply With Graham v. John Deere Co., 383 US 1 (1966)

In the recently published "Examination Guidelines For Determining Obviousness Under 35 U.S.C. 103 In View Of The Supreme Court Decision in KSR International Co. v. Teleflex, Inc.", (Federal Register/Vol. 72, No. 195/October 10, 2007/Notices) the U.S. PTO stated:

"To reject a claim based on this rationale, Office personnel must resolve the *Graham* \ factual inquiries. Office personnel must then articulate the following:

(1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;

(2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately;

(3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and

(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness."

As rationale for the above requirements the office relied upon the authority of KSR at 82 USPQ 2d at 1395 (2007); *Sakraida v. AG Pro, Inc.*, 425 US 273, 189 USPQ 449, 453 (1976); *Anderson's – Black Rock, Inc. v. Pavement Salvage Co.*, 396 US 57, 62-63, 163 USPQ 673, 675

(1969); and *Great Atl.& Pac. Tea Co. v. Supermarket Equip. Corp.* 340 US 147, 152, 87 USPQ 303, 306 (1950).

In the present case, it is respectfully and sincerely urged that the rejection based on Crawford, et al. in view of Howey, et al. utterly fails to comply with the requirement for a *Graham* factual inquiry as discussed above. Most important is the fact that these prior art references do not include each element claimed as pointed out above. Moreover, the rejection fails to make a finding that each element (lispro) would have performed the same function as (insulin) in the references. Further, the rejection fails to make a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable, i.e., that using iontophoresis and electroporation would affect the administration of a sufficient amount of the drug. Consequently, it is respectfully submitted that the rejection fails, as a matter of law, in view of the above authorities. Withdrawal of the rejection is respectfully requested.

Reconsideration is respectfully requested of the rejection of claims 3,4, 15-17 and 20 under 35 U.S.C. 103(a) as being unpatentable over Crawford, et al. in view of Howey, et al. in further view of Mori, et al.

The deficiencies of the Crawford, et al. and Howey, et al. references are discussed in detail above.

Recognizing the deficiencies of these references, as discussed above, the Examiner then relies on the additional secondary reference of Mori, et al. to cure these deficiencies. Although Mori, et al. disclose that insulin can be administrated with the combination of iontophoresis and electroporation, there is no disclosure whatever in Mori, et al. that the combined use of iontophoresis and electroporation could be used to successfully administer a sufficient amount of

lispro to a patient. On the contrary, that particular teaching comes only from the present application and constitutes an important element or aspect of the present invention.

Failing such a disclosure, it is respectfully submitted that Mori, et al. fail to cure the deficiencies of the Examiner's combination of Crawford, et al. and Howey, et al. Consequently, it is respectfully submitted that the rejection fails for the reasons set forth above. Withdrawal of the rejection is accordingly respectfully requested.

Reconsideration is respectfully requested of the rejection of claims 5-6 under 35 U.S.C. 103(a) as being unpatentable over Crawford, et al. in view of Howey, et al., and in further view of Jacobsen, et al.

The deficiencies of the Examiner's combination of Crawford, et al. and Howey, et al. are discussed above.

The Jacobsen reference, like the other references supplied by the Examiner, also fails to disclose administration of lispro by iontophoresis and electroporation. That teaching comes only from the present application and is in no way found in any of the references applied by the Examiner. Consequently, the Examiner would be justified in no longer maintaining the rejection. Withdrawal of the rejection is therefore respectfully requested.

Reconsideration is respectfully requested of the rejection of claims 7-10 and 18 as being unpatentable over Crawford, et al. in view of Howey, et al., and in further view of Mori, et al.

The combination of Crawford, et al. and Howey, et al. is discussed above.

The secondary reference of Mori, et al. fails to cure the deficiencies of the Examiner's combination of Crawford, et al. and Howey, et al. as discussed above. Consequently, the Examiner would be justified in no longer maintaining the rejection. Withdrawal of the rejection is accordingly respectfully requested.

Reconsideration is respectfully requested of the rejection of claims 11 and 19 as being unpatentable over Howey, et al. in view of Crawford, et al., in further view of Mori, et al., and in further view of Murdock.

The deficiencies of the Examiner's combination of Crawford, et al., Howey, et al., and Mori, et al. are discussed above in detail.

Although the Murdock reference does disclose the use of a dry drug in a reservoir in iontophoresis, Murdock fails to cure the deficiencies of the other references as discussed above, i.e., the administration of lispro using a combination of iontophoresis and electroporation. Consequently, the Examiner would be justified in no longer maintaining this rejection. Withdrawal of the rejection is accordingly respectfully requested.

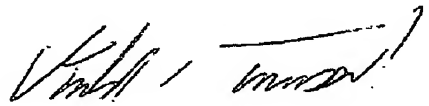
Reconsideration is respectfully requested of the rejection of claims 13 and 14 as being unpatentable over Crawford, et al., in view of Howey, in further view of Miller, et al., in further view of Murdock.

The deficiencies of Crawford, et al. and Howey, et al. are discussed above.

The Miller, et al. reference fails to cure the deficiencies of Crawford, et al. and Howey, et al., i.e., Miller, et al. fail to disclose the administration of lispro using iontophoresis and electroporation. The power supply of Miller, et al. fails to cure many of the basic deficiencies of the Examiner's other references. Consequently, the Examiner would be justified in no longer maintaining the rejection. Withdrawal of the rejection is accordingly respectfully requested.

In view of the foregoing, it is respectfully submitted that the application is now in condition for allowance, and early action and allowance thereof is accordingly respectfully requested. In the event there is any reason why the application cannot be allowed at the present time, it is respectfully requested that the Examiner contact the undersigned at the number listed below to resolve any problems.

Respectfully submitted,



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CERTIFICATE OF TRANSMISSION

I hereby certify that this 21-page Amendment in Docket No. MUR-043-USA-PCT, Serial No. 10/510,694, filed October 8, 2004, is being facsimile transmitted to the United States Patent and Trademark Office (Fax No. 571-273-8300) on April 28, 2008.

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Application No. 10/510,694
Amendment dated April 28, 2008
Reply to Office Action dated January 9, 2008
ANNOTATED SHEET SHOWING CHANGES

FIG. 5